The toxicokinetic data verified systemic exposures, however, because the sites were non-occluded it is not possible to determine how much material was absorbed through the skin or through the gut following oral ingestion. Maximum mean plasma concentrations (Cmax) of n-docosanol ranged from 15 ng/ml following exposure to the 0.4 % cream to 250 ng/ml in animals dosed with the 10 % cream (Table TK-3). Tmax occurred between 1.0 to 4.0 hours following topical administration. The terminal rate constants and the terminal half-lives could not be determined from the data collected in this study.

Table TK-3: Selected toxicokinetic data following a single dose (day 1) and daily dosing for 13 weeks (~ day 91) of n-docosanol in CD-1 mice.

	Day 1			Day 91		
C_{max} (ng/ml)	0.4%	2.0%	10%	0.4%	2.0%	10%
Males	20	27	225	-	-	205
Females	15	57	250	-	-	232

AUC_{0-24} (ng.h/ml)	0.4%	2.0%	10%	0.4%	2.0%	10%
Males	-	-	739	-	-	1390
Females	-	402	1140	-	-	1660

Concentrations of n-Docosanol below the limit of quantification (BLQ = <10 ng/ml) were entered as zero for calculation of means. If 50% of individual values (i.e. one of two values at each time point) were BLQ, the means were not calculated.

Study 41 - Subacute 28-Day Repeated-Dose Dermal Toxicology Study on Abraded Skin in Rabbits. Study report no. [redacted] 270382, *In life:* 7/25 to 9/10/90, conducted by [redacted] and [redacted] in compliance with GLP guidelines (OECD and 21 CFR 58). LIDAKOL batch nos. 211-112 and 214-11; and Placebo batch no. 214-12.

A draft report of this study was previously submitted under [redacted] submission N001, dated 7/16/91, and reviewed by Dr. Lauren Black, HFD-530, review dated 8/26/91. Her comments have been incorporated into this review.

Study Design: LIDAKOL 10 % Cream was applied to the abraded skin of New Zealand White rabbits for 28 consecutive days, followed by a 14-day recovery period. Animals, aged 12-15 weeks and weighing between 2.0 to 2.8 kg, were dosed with 0 (placebo cream, 10/sex), 50 mg (5/sex), 200 mg (5/sex), or 1000 mg/kg (10/sex) cream. Application sites were abraded at the beginning of the study and once weekly thereafter using a [redacted] which makes minor incisions through the stratum corneum but not into the dermis or at a depth which results in bleeding. The cream was applied in a uniform film over a shaved, abraded area of 2.5 cm^2 and covered with a semi-occlusive bandage for 6 hours/day. After 6 hours, the skin was washed gently with warm water and dried. Half the rabbits in each of the control and high dose groups (5/sex/group) were sacrificed on day 28; the remaining animals were observed for an additional 14-day recovery period prior to sacrifice. The following measures and evaluations were made: mortality, clinical signs, irritation of

the application site, food consumption, body weights, opthalmic exams, hematology, clinical chemistry (fasted at 4 & 6 weeks), organ weights, macroscopic necropsy observations, and histopathology. Organ weights were recorded for the brain, heart, liver, kidneys, adrenals, spleen and gonads. The following tissue samples were collected from all animals and fixed in 4% buffered neutral formaldehyde:

-adrenals
-aorta
-brain
-cecum
-colon
-duodenum
-epididymides
-esophagus
-eyes & optic nerves
-female mammary gland
-femur with joint
-harderian glands
-heart
-ileum
-jejunum
-kidneys
-larynx
-lachrymal gland
-liver
-lungs infused w/formalin
-lymph nodes (mandibular & mesenteric)
-nasopharynx
-ovaries
-pancreas
-pituitary
-prostate
-rectum
-salivary glands (mandibular & sublingual)
-sciatic nerve (left)
-seminal vesicles
-skeletal muscle
-skin (treated & untreated)
-spinal cord (cervical, midthoracic & lumbar)
-spleen
-sternum w/marrow
-stomach
-testes
-thymus
-thyroid & parathyroid
-tongue
-trachea
-urinary bladder
-uterus w/cervix
-vagina

Histopathology evaluations were only performed on the following tissues: adrenals, heart, kidneys, and liver from all control and high-dose animals terminated at both 4 and 6 weeks; treated and untreated skin from all animals; and gross lesions from all animals.

Review Comment: *Histopathology was performed on fewer than the recommended number of tissues and should have at least include gonads, brain, lung, and spleen. In addition, although gross lesions were examined histologically, the same tissues were not examined in other animals in either the same dosing group or in other groups to confirm that these lesions were incidental and were not microscopically present in other animals at lower or higher doses.*

Summary of Study Results: There were no mortalities, significant changes in food consumption or weight gain patterns, changes in opthalmic parameters, or clinical signs of toxicity in any of the groups during the treatment period. There was a higher incidence in local irritation effects in the controls and high-dose animals (slight erythema in ~50 % of the animals). Controls presented with minimal to slight general and focal erythema in up to 85 % of the males and <50 % of the females. About 50% of the animals also presented with edema. Both erythema and edema had subsided completely by the end of the 2-week recovery period, however, ~15-25 % of the control animals developed scaling during this time. There were no dermal effects noted in males dosed at 50 mg/kg and only slight erythema in <25 % of females during week 1. Males and females dosed with 200 mg/kg developed slight, transient erythema during weeks 1 and 3, respectively, of treatment. At 1000 mg/kg, slight erythema was evident in males primarily during week 1 (~50 %) of treatment and week 1 of recovery (<15 %); in females, minimal to slight erythema and edema were observed in <25 % of females beginning in week 2 and persisting through week 1 of the recovery period. Scaling was also noted in females during the recovery period, but was resolved by the end of the 2nd week.

Organ weights, either absolute or relative (brain and body weight ratios) were similar in all groups, with one exception, a decrease in liver weights at day 28 in all drug treated males. This effect appeared to be dose related, and resulted in a 13 % reduction in liver weight in the high-dose group relative to control. There was also one male in the high dose group which had a significant increase in AST and ALT, resulting in an increased group mean when compared to the control group. These

increases persisted through the recovery period, however, the significance of these increases in this animal is unknown. There were no changes in any of the hematologic parameters measured. One high-dose female showed a dark red discoloration under the application site, but this response was atypical of any other animal of this treatment group and did not correlated with any histopathological finding. At the end of the recovery period, females in the high-dose group had a slight drop in cholesterol and phosholipid concentration in blood. This drop was not statistically significant and is of questionable clinical relevance. There were no apparent drug-related histopathological changes or other signs of toxicologic effects from topical LIDAKOL application evident in this study following 4 weeks of treatment or the 2 week post-treatment recovery period.

Study 42 - Subacute 28-Day Dermal Tolerance Study with n-Docosanol (LIDAKOL) by Daily 6 Hours Administrations to the Intact and Abraded Skin of Rabbits. Study report no. [redacted] 107527 *In life*: 11/9 to 12/10/93, conducted by [redacted] with toxicokinetic sample analyses performed by [redacted] in compliance with OECD GLP guidelines. LIDAKOL Lot no. 153 (formulation 3, exp. date 6/1/94); placebo lot no. 152 (exp. date 6/1/94).

Study Design: A 5 day pilot study was performed between 10/25 and 10/30/93 with New Zealand White Rabbits (2/sex/group) to provide a basis for the selection of a treatment level for the 28 day topical study. As a result, a dose level of 1 g/kg/day was selected as the maximum amount of cream that could be applied to the skin of rabbits. 100 mg n-Docosanol (LIDAKOL 10 % Cream) was selected by the sponsor as the required active concentration.

Either test or placebo cream was applied to a shaved area of intact or abraded skin (3 rabbits/sex/group, age ~12 weeks, 2.0-3.0 kg) comprising approximately 10 % of the total body surface area (~120-140 cm^2). On day 1, the skin was abraded by making parallel caudalward scratches over the length of the exposure area with a sharp needle. This procedure was repeated during the study as soon as the scratches or lesions related to the scratches had visually disappeared. Test material was applied to a Metalline patch and left in contact with the skin 6 hours. After removal of the patch, residual test material was removed using tap-water and dry tissues. Animals were monitored for daily mortality, clinical signs of toxicity, and skin irritation; weekly for body weight; and clinical laboratory evaluations, necropsy and histology were performed at the end of the study. Blood samples for toxicokinetic evaluation were collected prior to treatment on study days 1, 7 and 28.

Organ weights were recorded for the adrenal glands, heart, kidneys, liver, spleen and testes. The following tissue samples were collected from all animals and fixed in 4 % buffered neutral formaldehyde:

-adrenals
-aorta
-brain
-cecum
-cervix
-clitoral gland
-colon
-duodenum
-epididymides
-esophagus
-eyes & optic nerves
-female mammary gland
-femur with joint
-gall bladder
-harderian glands
-heart
-ileum
-jejunum
-kidneys
-larynx
-lachrymal gland (exorbital)
-liver
-lung
-lymph nodes (mandibular & mesenteric)
-nasopharynx
-ovaries
-pancreas
-pituitary
-preputial gland
-prostate
-rectum
-salivary glands (mandibular & sublingual)
-sciatic nerve
-seminal vesicles
-skeletal muscle
-skin (treated & untreated)
-spinal cord (cervical,

midthoracic & lumbar)	-stomach	-thyroid & parathyroid	-urinary bladder
-spleen	-testes	-tongue	-uterus w/cervix
-sternum w/bone marrow	-thymus	-trachea	-vagina

Histopathology evaluations were only performed on the following tissues: adrenals, heart, kidneys, liver, spleen , treated and untreated skin area, testes and all gross lesions from all animals.

Summary of Study Results: There were no mortalities, observed clinical signs of toxicity (other than dermal irritation) or significant changes in weight gain during the study period. All animals, with the exception of 1 male and 1 female treated with LIDAKOL, showed minimal to slight erythema which was localized to the treated skin area. This erythema was accompanied by incidental edema and scabbing only in abraded areas. In general, dermal irritation was slightly more pronounced in placebo vs n-docosanol treated animals; and in abraded vs unabraded skin. Although concurrent untreated controls were not evaluated in this study, clinical laboratory results were compared to historical "normal" control data for New Zealand White rabbits of the same age. There were no significant differences in any hematologic (including PT and PTT) or serum chemistry parameter evaluated when compared between either placebo vs n-docosanol animals or treated animals vs historical controls. Lesions observed during necropsy, variations in organ weights, and histology findings were not considered to be treatment related. The small number of changes recorded in treated animals were within the range commonly seen for rabbits of this age and strain.

Toxicokinetics Evaluation: Plasma concentrations of n-docosanol ranged between <10 ng/ml (limit of detection) to 40.1 ng/ml.

Review Comments: *Unfortunately, measurable levels of n-docosanol were found in some of the animals from all dosing groups, including placebo, on each of the days tested. It must therefore be concluded that either 1) no true placebo was used in this study; 2) the animal area was contaminated with n-docosanol cream and all animals were exposed through ingestion; or 3) the method used for quanitation of n-docosanol in plasma is flawed. Samples from the above lots should be reanalyzed in order to validate the dermal portion of this study. All toxicokinetic results should be considered invalid and the results from this study suspect.*

Study 43 - A Penile Irritation Study in Rabbits with n-Docosanol 10 % Cream and n-Docosanol 12 % Cream. Study report no. SLS 3333.4, *In life:* 3/23 to 4/1/95, conducted by [redacted] in compliance with GLP guidelines (21 CFR 58). Batch nos. - 10% n-Docosanol Cream lot 223 (exp. date 11/7/96); 12% n-Docosanol Cream lot LP-149A (exp. date 3/3/96); 0.9% Sodium Chloride for Injection, USP lot 51259 (exp. date 10/96); and Gynol II with Nonoxynol-9 lot 24M710 (exp. date 10/97).

Study Design: This study was performed to assess the potential irritant and corrosive effects of n-Docosanol 10 % Cream and n-Docosanol 12 % Cream in the penile tissue of New Zealand White rabbits (age 7 months, 3.2-3.7 kg) when administered daily for 10 consecutive days. Four groups of male rabbits (10/group) were treated with ether 0.9 % NaCl solution, n-docosanol 10 % cream, n-docosanol 12 % cream, or a 1:1 (v/v) mixture of Gynol II with Nonoxynol-9 and n-docosanol 12 % cream. Using a 1 ml syringe, each rabbit was dosed once daily with 0.2 ml of the appropriate test or control article applied to the penis and surrounding prepuce. Collars were placed on each animal following the first and remained in place throughout the study period. Animals were examined daily

for signs of clinical toxicity and scored for penile irritation according to Draize; body weights were recorded upon receipt of the animals and on days -1 and 10 of the study; and histopathology was performed on the penis and surrounding prepuce.

Summary of Study Results: There were no significant clinical abnormalities during the study or changes in body weight over the course of the study. Very slight erythema (grade 1) was observed more frequently in the animals treated with n-Docosanol 12 % Cream. Microscopic examination of the penile mucosa and penile urethra revealed no evidence of drug related irritation. Occasional lympocytic and/or polymorphonuclear submucosal or intra-epithelial infiltrates and/or focal areas of recent submucosal hemorrhage were observed, they occurred with approximately equal frequency in control rabbits as in treated animals and were judged to have been unassociated with treatment.

Study 44 - A Vaginal Irritation Study in Rabbits with n-Docosanol 10 % Cream and n-Docosanol 12 % Cream. Study report no. [redacted]3333.3. *In life:* 3/23 to 3/31/95, conducted by [redacted] in compliance with GLP guidelines (21 CFR 58). Batch nos. - 10% n-Docosanol Cream lot 223 (exp. date 11/7/96); 12% n-Docosanol Cream lot LP-149A (exp. date 3/3/96); 0.9% Sodium Chloride for Injection, USP lot 51259 (exp. date 10/96); and Gynol II with Nonoxynol-9 lot 24M710 (exp. date 10/97).

Study Design: This study was performed to assess the potential irritant and/or corrosive effects of n-Docosanol 10 % Cream and n-Docosanol 12 % Cream in the vaginal tissue of virgin New Zealand White rabbits (age 4 months, 2.5-3.1 kg) when administered daily for 10 consecutive days. Five groups of female rabbits (10/group) were treated with ether 0.9 % NaCl solution, Gynol II with Nonoxynol-9, n-Docosanol 10 % Cream, n-Docosanol 1% Cream, or a 1:1 (v/v) mixture of Gynol II with Nonoxynol-9 and n-Docosanol 12 % Cream. Using a 1 ml syringe, each rabbit was dosed once daily with 1 ml of the appropriate test expressed directly into the vaginal vault. Animals were examined twice daily for signs of clinical toxicity; body weights were recorded upon receipt of the animals and on days -1 and 10 of the study; and the uterus, ovaries, vagina and cervix were removed and examined macroscopically. Organ weights were recorded for the uterus and ovaries and the vagina and cervix were opened longitudinally and evaluated for irritation using Draize scoring. Histopathology was performed on the 3 approximate 1 cm x 0.2 cm sections of the fixed vaginal tissue (one section each from the cranial, medial and caudal areas) and any other gross lesions noted at necropsy.

Summary of Study Results: All females survived to scheduled euthanasia. There were no clinical signs of toxicity in any of the groups or differences in weight gain between groups. Uterine and ovarian organ weights were similar between groups. Macroscopic evaluation of the vaginal tissue for irritation resulted in scores ranging from very slight (grade 1) to moderate/severe (grade 3) erythema and edema. These responses generally occurred in all groups but there was an apparent dose related increase in overall scores in the animals treated with n-Docosanol Cream. Histopathological evaluation of the vaginal tissue resulted in composite irritation scores of 1.2 for the 0.9 % NaCl solution; 2.3 and 2.7 for the n-Docosanol 10 % and 12 % Creams, respectively; and 6.1 and 6.0 for the Gynol II with Nonoxynol-9 and the 1:1 mixture of Gynol II with Nonoxynol-9 and n-Docosanol 12 % Cream, respectively. Scores between 1 and 8 are deemed acceptable levels for vaginal irritation (1-4 minimal, 5-8 mild, 9-11 moderate, and 12-16 marked irritation).

Study 45 - Rabbit Vaginal Toxicology Study (28-Day) with Gas Chromatographic Analysis of Plasma From LIDAKOL Treated Rabbits. Study report no. [redacted]427-LK-001-91. *In life:* 9/12 to 10/8/91, conducted by [redacted] in compliance with GLP guidelines (21 CFR 58). LIDAKOL 20% Cream - Lot no. 254L-39.

Study Design: This study was designed to evaluate the toxicity of n-Docosanol 20% Cream when administered to the vaginal mucous membranes in New Zealand White female rabbits. n-Docosanol 20% Cream was applied twice daily to both vulvar lips of 5 female rabbits at a dose of 0.25 ml/lip (1.0 ml/day/animal) for 28 days. Deionized water, at the same dose volume, was applied to 2 control animals. Rabbits were weighed on the first day of dosing and at termination. During the treatments, signs of irritation and discharge were evaluated prior to each dose. Clinical observations were recorded daily and blood samples were collected on days 1, 14 and 28 at 1, 4 and 8 hours after the morning dose for toxicokinetic analysis. Approximately 24 hours after the last dose, the rabbits were sacrificed and a gross necropsy was performed. Treated and untreated sites were examined histologically and scored for irritation.

Summary of Study Results: There was one death (1/5) on day 16 in the treated animals. This animal evinced decreased activity and reduced food consumption and fecal output on day 15, and at necropsy presented with distended and fluid filled intestines, ascites and distended cecum. These observations were not believed to be drug related. There were no other clinical signs of toxicity observed in any of the other control or treated animals during the study period. Macroscopic evaluation of treatment sites did not revealed noticeable signs of irritation or discharge in control or treated animals. Histopathological evaluation included examination of the epithelium, leukocyes, congestion and edema of the distal vagina. Minimal irritation of distal vagina was observed in both control animals and in 3/4 n-docosanol treated animals; mild irritation was observed in the 4th animal. The mean irritation scores for control and treated animals were 2.5 and 4.0, respectively.

Analytical Report GC Analysis of 1-Docosanol in Rabbit Plasma: Systemic exposure following topical application to the vulvar lips of female rabbits was minimal. Rabbit plasma samples were analyzed by [redacted] Levels of n-docosanol in the plasma were generally below the limit of quanitation (10 ng/ml). Each dosed animal had at least one sample with n-docosanol levels >10 ng/ml. Readings ranged between 11.0 to 13.4 ng/ml at 4 hrs on day 1; 10.7 to 20.9 ng/ml at 8 and 4 hrs, respectively, on day 14; and a single reading of 12.8 ng/ml at 4 hrs on day 28. The plasma concentrations which did register above the level of detection represent a combination of absorbed material from the vaginal tissues as well as from the gut following oral ingestion during grooming.

Reproductive and Developmental Toxicology Study Reviews

Study 46 - An Oral Dose Range-finding Fertility and Pre- and Post-natal Development Study of n-Docosanol Suspension in Rats. [redacted] study report no. 94/LAK003/0898. *In life:* 5/31 to 7/25/94, conducted at [redacted] in compliance with GLP guidances OEDC and 21 CFR 58. n-Docosanol batch no. 6232.

Study Design: Stock n-docosanol solutions were prepared as a 20 % aqueous suspension in [redacted] batches as needed. Adult virgin male and female Sprague Dawley CD rats (6/sex/group, ages 10-11 weeks, weighing 315-370 g and 216-250 g, respectively) were treated with by oral gavage with 500, 1000 and 2000 mg/kg/day n-docosanol or with vehicle beginning 15 days prior to pairing and throughout pairing. Males continued treatment until termination and females were treated throughout gestation and lactation until termination on day 4 of lactation. During treatment, all animals were monitored for clinical signs of toxicity, bodyweight, food and water consumption and female estrous cycling. Females were permitted to deliver their young naturally and rear their own offspring until day 4 of lactation. Parturition and duration of gestation were recorded. Terminal litter observations included number of offspring, fetal bodyweight, sex ratio and health of offspring. Males were terminated after successful parturition by the females, while the females and offspring were euthanized on day 4 of lactation. All animals were examined externally and internally for macroscopic abnormalities.

Review Note: *An error was made in preparing the 20% solution (w/v was used rather than w/w) which resulted in a 7% lower dose than called for in the protocol. This error was consistent and resulted in proportionately smaller doses for all dosing levels, e.g. doses of 465, 930 and 1860 mg/kg/day instead of 500, 1000 and 2000 mg/kg/day, respectively.*

Summary of Study Results: The general condition of all animals appeared to be unaffected by treatment. One female dosed at 1000 mg/kg/day was found dead after four days of treatment. Necropsy findings suggested that the death may have been associated with the dosing procedure and was unrelated to n-docosanol toxicity. There was a slight, nonsignificant, dose-related decrease in overall bodyweight gain in treated males when compared to controls (15 % at 1860 mg/kg/day). There were no significant difference in estrous cycles, mating performance and fertility, gestation length, parturition and fertility in treated animals. Two pairings in the 1930 mg/kg/day group failed to achieve pregnancy, however, in the absence of any effects in the 1860 mg/kg/day group, these results were not considered a result of n-docosanol treatment. The general condition of offspring, litter size, survival, and sex ratio were similar in all groups. Absolute body weights of offspring from animals treated at 1860 mg/kg were slightly lower than concurrent controls, however, body weight gains to day 4 were unaffected. There were no gross treatment-related findings noted at necropsy of both the F0 and F1 generations.

Based on the study results, 2000 mg/kg/day was considered suitable as the high dose for the main pre- and post-natal study in rats.

Study 47 - An Oral Dose Range-finding Embryo-Fetal Development Study of n-Docosanol Suspension in Rats. [redacted] study report no. 94/LAK004/0675. *In life:* 5/23 to 6/15/94, conducted at [redacted] in compliance with GLP guidances OEDC and 21 CFR 58. n-Docosanol batch no. 6232.

Study Design: Stock n-docosanol solutions were prepared twice weekly as a 20 % aqueous suspension in [redacted]. Presumed pregnant Sprague Dawley CD rats (6/group, ages 10-11 weeks, weighing 216-251 g) were dosed by oral gavage from day 6 to day 15 inclusive of gestation with either vehicle or n-docosanol suspension of 500, 1000 or 2000 mg/kg/day. During treatment, animals were monitored for clinical signs of toxicity, maternal bodyweight, food and water consumption. All females were euthanized on day 20 of gestation and examined macroscopically for any signs of toxicity. Terminal evaluation for embryo-fetal development included quantification of the numbers of corpora lutea in each ovary, implantation sites, resorption sites, fetuses in each uterine horn; weight and sex of individual fetuses; individual placental weights; and examination of all fetuses for external abnormalities and approximately 50 % of fetuses for gross internal abnormalities.

Review Note: *An error was made in preparing the 20% solution (w/v was used rather than w/w) which resulted in a 7% lower dose than called for in the protocol. This error was consistent and resulted in proportionately smaller doses for all dosing levels, e.g. doses of 465, 930 and 1860 mg/kg/day instead of 500, 1000 and 2000 mg/kg/day, respectively.*

Summary of Study Results: The general condition, weight gain, food and water consumption and necropsy results of all treated animals were similar to the controls and showed no adverse effects of treatment. One control female was *killed in extremis* on day 16 of gestation, exhibiting hunched posture and piloeretion in association with bodyweight loss of 35 g over 48 hours. Necropsy revealed 14 late resorptions *in utero* and the vagina contained red mucoid material.

Litter responses, as assessed by numbers of corpora lutea, implantations and viable fetuses, resorption sites, and placental weights were similar in all groups and showed no adverse effects of maternal treatment with n-docosanol. The mean fetal weights from dams treated with 2000 mg/kg/day were slightly lower than the concurrent controls but were not statistically significant and fell within the historical control ranges. However, the mean number of viable young (15.3) from this group was greater than the other groups (control = 13.8), possibly accounting for the slightly lower mean fetal weight. Bilateral increased renal pelvic cavitation and hyroureter was observed in approximately 18% of the fetuses, affecting 3/6 litters, from dams in the 500 mg/kg/day group. However, since this effect was not observed in fetuses from either of the two higher dose groups it was considered unlikely to be related to maternal treatment with n-docosanol.

Based on the results of this study, a high dosage of 2000 mg/kg/day was considered appropriate for the main combined fertility and teratology study in rats.

Study 48 - A Combined Fertility, General Reproductive Performance, and Embryo-Fetal Development Study of Orally Administered n-Docosanol Suspension in Rats. [redacted] study report no. 95/LAK009/0615. *In life:* 12/13/94 to 4/5/95, conducted at [redacted] in compliance with GLP guidelines OEDC and 21 CFR 58 and in accordance with the ICH guidelines. Fetal pathology was performed by [redacted] n-Docosanol batch no. 52201.

Study Design: The influence of n-docosanol on reproductive function, fertility and embryo-fetal development was assessed in groups of sexually mature male and female Sprague Dawley CD rats. Groups of 22 rats/sex/group (males: ages 10-11 weeks, weighing 208-262 g & females ages 6-7 weeks, weighing 193-240 g) were administered 0, 10, 100, or 1000 mg/kg/day n-docosanol in [redacted] aqueous suspensions. The males were dosed for 71 days before pairing, throughout pairing, and until termination following necropsy of the females. The females were dosed daily from 15 days prior to pairing through day 17 after mating. Females were euthanized on day 20 after mating for examination of their ovaries and uterine contents. Necropsies in both sexes involved macroscopic inspections.

Summary of Study Results:

Adult Animals: One male, dosed at 1000 mg/kg/day, was euthanized for humane reasons during week 6 of treatment after exhibiting abdominal distention, pallor, ptosis, irregular respiration and weight loss. Necropsy findings included watery blood, enlargement of the liver with the lobular pattern accentuated, an enlarged pale spleen and reduced gastro-intestinal tract content. Since this was the only death in the study and no toxicity was observed in other animals, investigators did not considered it to be drug-related. There were no other significant differences between treated animals and controls or between treatment groups in clinical behavior and appearance; bodyweight gain, food and water consumption; female estrous cycling; sperm morphology, motility and numbers; mating behavior and fertility; and gross appearance of reproductive organs (and relative weights) and internal tissues at necropsy.

Litter Parameters: Litter parameters (number of corpora lutea in each ovary, number of implantation sites, number of early and late resorption sites, and the number, sex ratio and distribution of fetuses in each uterine horn), fetal survival, and fetal growth were all comparable between treatment groups, concurrent controls, and/or historical control ranges. With the exception of 3 fetuses, morphological development (including visceral and skeletal) in fetuses appeared normal. The 3 fetuses had notable findings: one fetus from the 100 mg/kg dosing group (dam 154) had small eye orbits consistent with agenesis of the eyes; one fetus from the 1000 mg/kg dosing group (dam 175) had a retro-esophageal right subclavian artery with an associated misshapen thymus gland; and another fetus from the 1000 mg/kg dosing group (dam 176) had cleft and imcomplete basisphenoid and basioccipital bones. These incidences were isolated, did not appear to be dose-related, and/or were within the incidence rates reported for the historical controls. Under the condition of this study, n-docosanol was not considered to adversely affect reproduction or to be teratogenic.

Review Note: Quality control of dosing solutions revealed that the dose solutions for the 10 and 100 mg groups at weeks 5 and 9 were lower than expected. However, all high dose solutions (1000 mg) were within study limits. Therefore the importance of this deviation in protocol is considered inconsequential to the study results.

Study 49 - A Pre- and Post-natal Development Study of Orally Administered n-Docosanol Suspension in Rats. Study report no. 95/LAK011/0841. *In life:* 12/20/94 to 4/24/95, conducted at [redacted] in compliance with GLP guidelines OEDC and 21 CFR 58 and in accordance with the ICH guidelines. n-Docosanol batch no. 52201.

Study Design: The objective of this study was to assess the effects of repeated oral administration of n-docosanol on pre- and post-natal development in the Sprague Dawley rat. Four groups (22 females/group) of presumed pregnant F0 female rats (ages 10-11 weeks, weighing 243-283 g) were dosed with 0, 10, 100 or 1000 mg/kg/day n-docosanol [redacted] from day 7 after mating to day 20 of lactation. All females were allowed to give birth naturally and rear their offspring to weaning at day 21 of lactation. F0 females were monitored pre- and post-natally for clinical signs of toxicity, bodyweight gain, food and water consumption, and partuition and length of gestation. Litters were monitored number of live and stillborn births, body weight, and sex ratios. Development of culled (8 pups/dam) F1 offspring was evaluated by monitoring clinical signs and behavior, mortality, physical development (pinna unfolding, hair growth, tooth eruption, eye opening, vaginal opening, balanopreputial separation), auditory and visual function, activity, learning ability, and neuromuscular function (traversing flat and round rods, rotarod treadmill, mid-air righting reflex; fore- and hind-limb wire-hanging, and grid-gripping ability). At approximately 5 weeks of age, 20 males and 20 female F1 rats from each group were evaluated for physical and sexual maturation and reproductive performance. F1 females were killed on day 14 after mating for examination of ovaries and uterine contents. Gross necropsies were performed on all F0 females, F1 offspring, and F2 fetuses.

Summary of Study Results:

F0 Females: One control animal was euthanized on day 4 of lactation following the death of her offspring. Macroscopic examination revealed that the mammary tissue was pale and inactive. Another female in the 100 mg/kg dose group was found dead on day 5 of lactation having shown no clinical signs of illness. Necropsy revealed cyanosis of the extremities, red/yellow fluid and pale amorphous tissue in the thoracic cavity, pulmonary congestion and reduced, dehydrated cecal contents. The cause of death was considered unrelated to treatment. There were no changes in body weight, food and water consumption, gestation length, parturition, or lactation in n-docosanol treated animals.

F1 Offspring: The general condition of offspring was similar in all groups with no apparent adverse effects of maternal treatment with n-docosanol. Litter sizes, sex ratios, birth weights and survival rates were similar to controls. There were no dose-related differences in weight gain, physical development, auditory and visual responses, learning ability, or neuromuscular function. A small number of males and females in the treated groups failed to mate or failed to achieve pregnancy. However, the mating rate, conception rate and fertility index values were within, or close to, the historical control ranges.

Necropsies of animals which died prior to termination, F1 animals terminated at the time of weaning and mated F1 males and females terminated on day 14 of gestation, revealed no adverse effects which were linked to n-docosanol treatment. The numbers of corpora lutea, implantations, viable young and resorptions for F1 females were comparable to both concurrent controls and historical values.

Review Note: *Quality control of dosing solutions revealed that the dose solutions for the 10 and 100 mg groups at weeks 5 and 9 were lower than expected. However, all high dose solutions (1000 mg) were within study limits. Therefore the importance of this deviation in protocol is considered inconsequential to the study results.*

[redacted]

Study 51 - An Oral Dose Range-finding Study of n-Docosanol Suspension in Rabbits. Study report no. 94/LAK005/0588. *In life:* 5/16 to 6/14/94, conducted at [redacted] in compliance with GLP guidelines OEDC and 21 CFR 58. n-docosanol batch no. 6232.

Study Design: Rising doses of n-docosanol suspension were administered by oral gavage to 2 non-pregnant New Zealand White rabbits (group 1, ages 18-26 weeks, weighing 4.11 to 4.38 kg) over 8 days, commencing at an initial dose of 250 mg/kg/day until a maximum dose of 2000 mg/kg/day was achieved (2 day increments of 250→500→1000→2000). Two females (group 2) were then inseminated and received n-docosanol at a dose of 2000 mg/kg/day for 7 consecutive days from day 6 to day 12 of gestation. Animals were monitored for clinical signs of toxicity and body weight changes, and ~24 hours following completion of treatment all animals were euthanized and examined macroscopically for adverse reactions to treatment.

Review Note: *An error was made in preparing the 20% solution (w/v was used rather than w/w) which resulted in a 7% lower dose than called for in the protocol. This error was consistent and resulted in proportionately smaller doses for all dosing levels, e.g. doses of 232.5, 465, 930 and 1860 mg/kg/day, respectively.*

Summary of Study Results: The body weight gains and general condition of pregnant and nonpregnant female rabbits were unaffected by treatment with n-docosanol. No macroscopic changes were seen at necropsy. Implantations appeared normal by gross observation. It was concluded that 2000 mg/kg/day was appropriate for use in the dose range-finding embryo-fetal study in rabbits.

Study 52 -A Dose Range-finding Embryo-Fetal Development Study of Orally Administered n-Docosanol Suspension in Rabbits. Study report no. 94/LAK007/1115. *In life:* 7/5 to 7/28/94, conducted at [redacted] in compliance with GLP guidelines OEDC and 21 CFR 58. n-Docosanol batch no.6232.

Study Design: The objective of this preliminary investigation was to examine the effects of repeated oral administration of n-docosanol during the organogenesis phase of gestation and on the progress and outcome of pregnancy in New Zealand White rabbits; and to establish suitable dosages for use in the main embryo-fetal development study (LAK010). Rabbits (4/group, ages 19-27 weeks, weighing 3.49-4.83 kg) were treated by oral gavage from gestation day 6 to 29, inclusively, at n-docosanol dose levels of 0, 500, 1000 or 2000 mg/kg/day. Animals were monitored for clinical signs of toxicity, bodyweight gain, and food and water consumption. The animals were euthanized on day 29 of gestation and gross necropsies performed. Ovaries and uterine contents were examined for the number of corpora lutea, number of implantation sites, number of resorption sites, number and distribution of fetuses, and fetal and placental weights.

Review Note: *An error was made in preparing the 20% solution (w/v was used rather than w/w) which resulted in a 7% lower dose than called for in the protocol. This error was consistent and resulted in proportionately smaller doses for all dosing levels, e.g. doses of 465, 930 and 1860 mg/kg/day, respectively.*

Summary of Study Results: One control female died as a result of the dosing procedure. Other than pale feces observed in animals receiving 1860 mg/kg/day (probably related to unabsorbed drug), the general condition of the dams and offspring were unaffected by treatment with n-docosanol. The group mean numbers of corpora lutea, implantations and viable young in high dose females (2000 mg/kg/day) appeared low in comparison with the controls. This was considered to be due to one animal which had unilateral implantation. Exclusion of this animal from the group means gave values similar to those of the control.

It was concluded that 2000 mg/kg/day would be a suitable dose as the highest dosage for use in a main teratology study in the rabbit.

Study 53 - An Embryo-Fetal Development Study of Orally Administered n-Docosanol Suspension in Rabbits. Study report no. 95/LAK010/0760. *In life:* 5/9 to 6/14/94, conducted at [redacted] in compliance with GLP guidelines OEDC and 21 CFR 58. n-Docosanol batch no. 52201.

Study Design: The effects of n-docosanol on the progress and outcome of pregnancy were assessed in sexually mature New Zealand White female rabbits (22/group, ages 19-27 weeks, weighing 3.29-4.98 kg). Rabbits were treated daily by oral gavage with aqueous solutions of [redacted] containing 0, 125, 500 or 2000 mg/kg n-docosanol from day 6 through day 29 of gestation. Animals were monitored for clinical signs of toxicity, bodyweight gain, and food and water consumption; and gross necropsies were performed after termination on day 29 of gestation. Ovaries and uterine contents were examined for the number of corpora lutea, number of implantation sites, number of resorption sites, number and distribution of fetuses, and fetal and placental weights.

Summary of Study Results: One control female delivered prematurely on day 29 of gestation after exhibiting marked weight loss and low food and water intake at the end of the gestation period. Seven live and ten dead fetuses were found; at least two of the dead fetuses were considered to have been alive at birth. There were no other effects on the overall condition of the other animals, with the exception of pale feces observed in the majority of females receiving 2000 mg/kg n-docosanol/day. Weight gain, food consumption, necropsy results and litter parameters were comparable between groups: 3 females (1 control, 1 dosed with 125 mg/kg and 1 dosed with 500 mg/kg) showed early total litter loss. Fetal anomalies (visceral and skeletal) observed in treated litters at necropsy were similar in both type and frequency to the concurrent control and/or the historical control data from the laboratory and were not dose-related. Therefore, the no observed adverse effect level (NOAEL) in this study was considered to be 2000 mg/kg/day.

Study 54 - A Fertility and General Reproduction Study in Rabbits with n-Docosanol 12% Cream. Study report no. SLS 3333.2. *In life:* 3/23 to 4/3/95, conducted at [redacted] in compliance with GLP guidelines 21 CFR 58. 12% n-Docosanol Cream lot no. LP-149A; K-Y® Jelly (control material) lot no. 2574L, exp. date 8/97.

Study Design: This study was performed to determine and evaluate the toxic potential of n-docosanol when administered intra-vaginally as a 12% cream (formulation 3) on the reproductive capabilities of female New Zealand White rabbits. Virgin rabbits (aged ~5.5 months, weighing 2.8-3.7 kg) were treated with a single dose, placed into the vaginal vault, of 1 ml of either n-docosanol 12% cream or control (K-Y Jelly®) prior to mating. Approximately 5 minutes following treatment, females were allowed to mate naturally with proven breeder males. Does were allowed to stay with the buck for approximately 30 minutes after mating and then treated with 100 I.U. of human chorionic gonadotropin, via the marginal ear vein. If copulation did not occur within approximately 20 minutes, the doe was placed in the cage of another buck and the mating process repeated. The first 16 females in each group that were treated and successfully mated were utilized for the study. Parameters evaluated during the study included clinical observations, body weights, and food consumption. All females were euthanized on gestation day 10 and dams and fetuses were subjected to gross necropsy. The ovaries and uterus were removed and the number of corpora lutea, number of implantation sites, number of resorption sites, number and distribution of fetuses, and fetal and placental weights were recorded.

Summary of Study Results: Vaginal administration of n-docosanol 12% cream prior to mating did not appear to have a significant effect on either the copulation index or the fertility of rabbits. No maternal toxicity as assessed by clinical observations, weight gain and changes in food consumption was observed during the study. There were no significant differences in the mean number of corpora lutea, early resorptions or post-implantation sites between the two treatment groups. However, there was a significant difference in the number of viable fetuses and implantation sites in the n-docosanol group compared to the K-Y Jelly group due to a statistically significant increase in the mean pre-implantation loss in the n-docosanol group (see Table below). Among the 11/16 gravid females in this group, 2 does had 1 implant each; 1 doe had 2 implants; and another doe had four implants while the number of corpora lutea in these females was comparable to the animals in the control group. These results indicated that these females ovulated normally but only a few of the ova were

fertilized, or if fertilization did occur, only a few of the fertilized eggs were successfully implanted, or a combination of both occurred. Since a majority of the does in this group did have implants and live fetuses comparable to the controls, it could not be determined whether the n-docosanol treatment may have had an effect on the sperm or the fertilized eggs which resulted in this increase in pre-implantation loss observed in 4 does.

Parameter	K-Y Jelly	12 % n-Docosanol
Copulation Index	100 %	80.0 %
Fertility Index	87.5 %	68.8 %
Mean numbers of -		
Corpora Lutea	10.1	11.4
Implantation Sites	7.6	5.5
Pre-implantation Loss	2.5	5.8 *
Viable Fetuses	7.4	5.5
Early Resorptions	0.2	0.1
Post-implantation Loss	0.2	0.1

* p = <0.05 (two-tailed nonparametric Mann-Whitney U test)

Certificate of Analysis: n-Docosanol 12% Cream was analyzed by [redacted] and was found to comply with protocol specifications (10.8-13.2% w/w n-docosanol).

Genotoxicity Study Reviews (GLP)

The following genotoxicity studies were performed by [redacted] in compliance with OECD GLP guidelines. All assays were conducted with n-docosanol, batch no. BRL C22 - 6/28/89; test material for the *in vitro* assay was dissolved in ethanol and for the *in vivo* assay in polyethylene glycol (PEG).

These studies were previously submitted under [redacted] submission N001, dated 7/16/91, and reviewed by Dr. Lauren Black, HFD-530, review dated 8/26/91.

Study 55 - *Salmonella typhimurium* Mutation Assay with LIDAKOL. Report no. [redacted]170010, *In life:* 11/14 to 12/4/89.

Study Design: This study was designed to elucidate the potential for n-docosanol to induce gene mutations in Salmonella Typhimurium, tester strains TA 1535 (base pair), 1537, 1538, 98, and 100 (base pair). The n-docosanol was evaluated at 10 - 1000 µg/ml, with and without the S9 liver microsomal fraction (derived from rat liver). All data points were performed in triplicate and the experiment was performed twice. Controls consisted of ethanol, sodium azide, 2-aminoanthracene, or 4-nitro-o-phenylene-diamine.

Summary of Study Results: n-Docosanol did not induce point mutations by base pair changes or frame shifts in the strains used. No increase in mutation rate (number of revertants) was measured. Positive controls performed as expected.

Study 56 - Gene Mutation Assay in Chinese Hamster V79 Cells *in vitro* with LIDAKOL. Report no. [redacted]170021, *In life:* 10/20 to 12/18/89.

Study Design: This study was performed to evaluate the potential of n-docosanol to induce gene (point) mutations at the HGPRT locus in V79 cells of the Chinese hamster *in vitro*. Two independent experiments were performed in the presence and absence of S9 microsomal liver fraction, and tested 2 - 20 µg/ml (limit of solubility) of n-docosanol. A positive result was scored if the test article triples the spontaneous mutation frequency. Control substances were ethanol, ethylmethanesulfonate (1 mg/ml), and 7,12-dimethylbenz(a)anthracene (15.4 µg/ml). Two independent experiments were performed with positive controls performing as expected.

Summary of Study Results: There were no signs of cytotoxicity or changes in the gene mutation rate at the HGPRT locus with any of the doses.

Study 57 - Chromosome Aberration Assay in Chinese Hamster V79 Cells in vitro with LIDAKOL. Report no. [redacted]170032, *In life:* 1/29 to 3/8/90.

Study Design: The ability of n-docosanol (in ethanol) to induce structural chromosome aberrations in Chinese hamster V79 cells was evaluated *in vitro* over a dose range of 0.6 - 20.0 µg/ml, with and without S9 metabolic activation. Metaphase spreads were prepared and scored for structural chromosome aberrations following 7, 18, and 28 hours of incubation with n-docosanol. Controls consisted of ethanol, ethylmethanesulfonate (0.72 mg/ml), and cyclophosphamide (1.4 µg/ml).

Summary of Study Results: Treatment with 20 µg/ml n-docosanol did not reduce the plating efficiency of the V79 cells or the mitotic index. There were no relevant increases in cells with structural aberrations after treatment with n-docosanol at any fixation interval, either in the presence or absence of liver S9 mix. Positive controls performed as expected.

Study 58 - Micronucleus Assay in Bone Marrow Cells of the Mouse with LIDAKOL. Report no. [redacted]170043, *In life:* 11/20/89 to 3/28/90.

Study Design: This study evaluated the potential for n-docosanol to induce micronuclei in polychromatic erythrocytes (PCE) in the bone marrow of the NMRI mouse. Fasted NMRI mice were treated with 50, 150, and 500 mg/kg n-docosanol administered by oral gavage at a volume of 10 ml/kg n-docosanol suspended in PEG. Five (5) mice/sex/group were sacrificed at intervals of at 24, 48, and 72 hours following treatment and femoral bone marrow cells harvested. To describe a cytotoxic effect, the ratio between polychromatic and normochromatic erythrocytes was determined at each sampling point and expressed as normochromatic erythrocytes/1000 polychromatic

erythrocytes (NCE/PCE). To describe a genotoxic effect, the number of cells with micronuclei were counted/1000 polychromatic cells. Slide analysis was performed with coded slides. Controls consisted of PEG and cyclophosphamide (40 mg/kg).

Summary of Study Results: Increased frequency of micronuclei was not detected at any dose level or interval examined following treatment with the n-docosanol. There were no significant differences in group means for NCE/PCE ratios between groups, although the ratios did decrease slightly over time (e.g. ↓NCE, ↑PCE). Controls performed as expected.

Review Note: *The appearance of "slight toxic reactions" e.g. "eyelid closure and apathy" was used for proof of absorption. PK data was not submitted to confirm systemic exposure.*

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HUMAN PHARMACOKINETIC DATA

[The data presented below was taken from the Sponsor's Summary Data. The Biopharmacology Review should be referred to for definitive human pharmacokinetic data.]

In a preliminary study [Study IRAD 040-003], LIDAKOL (300 mg, Formulation 1) was applied to the underside of the right forearm 4 times/day for 7 days. n-Docosanol concentrations were below the limit of quantification (<3 µg/ml) in all blood samples collected. Similar results were observed when LIDAKOL cream (90 mg/dose) was administered 5 times/day for 2 days to otherwise healthy patients experiencing a recurrence of herpes labialis: n-Docosanol concentrations were below the limit of quantification (<10 ng/ml) in all blood samples collected except one which was measured at 10 ng/ml [Clinical Study 95-LID-01].

Plasma levels of n-docosanol were detectable following oral administration of single doses of 1 and 5 g/kg n-docosanol solutions to healthy male subjects [n=5, Clinical Study 94-LID-02]. Selected pharmacokinetic parameters are presented below:

Parameter	1 g Dose		5 g Dose	
	Mean	Range	Mean	Range
Cmax (ng/ml)	19 ± 18		124 ± 120	
Tmax (hr)	8		6	
AUC, 0-48 hr (ng.h/ml)	172 ± 211		713 ± 829	
Cl_{po}/F (L/min)	33 ± 397		410 ± 609	

Elimination of n-docosanol in healthy male subjects was also examined using a single oral dose of ^{14}C-labeled n-docosanol in [Clinical Study 95-LID-01]. The primary route of elimination was in the feces, presumably as unabsorbed material.

% of Actual Dose (n=6) Found in -	Mean	Range
Urine	0.028 ± 0.0490	
Feces	103.73 ± 3.960	
Air	0.907 ± 0.400	
Total	104.68 ± 3.990	

Taking into account both oral and dermal absorption of n-docosanol following applications to the lips, the Sponsor has estimated the maximum human plasma concentrations, following multiple therapeutic topical doses to the lips, to be approximately 0.3 to 0.4 ng/ml.

SUMMARY AND DISCUSSION

n-Docosanol is a long chain alcohol which is intended for use as the active ingredient in LIDAKOL® 10% Cream. LIDAKOL® is being developed for the treatment of recurrent oral-facial herpes simplex lesions. n-Docosanol does not appear to have direct anti-viral activity. The proposed pharmacodynamic basis of action appears to be as an inhibitor of replication in lipid-enveloped viruses. Following bioactivation, n-docosanol appears to block fusion of lipid-enveloped viruses with cell membranes, thus inhibiting cellular entry, nuclear localization, and subsequent viral replication. *In vitro* studies found it to be equally effective against wild type, clinical isolates and acyclovir resistant mutants of the Herpes Simplex Virus (HSV).

The upper estimate of the anticipated daily dose of n-docosanol for treatment of oral herpes is 0.5 to 1.0 mg/kg body weight (5 applications of 50 to 100 mg 10% n-docosanol cream per 50 kg body weight). In the treatment of herpes labialis, systemic exposures to n-docosanol are likely to occur through dermal absorption as well oral ingestion. The Sponsor has estimated the total human systemic dose following multiple therapeutic topical doses to be approximately 0.3 to 0.4 ng/ml.

Safety pharmacology studies in mice and rats administered oral doses of $\leq$1000 mg/kg n-docosanol demonstrated no significant effects on any of the following parameters tested: general or clinical behavior, locomotor activity, thiopental-induced sleeping time, synergistic or antagonistic convulsant activity, or intestinal charcoal transport (*male mice*); and normal body temperature or urinary volume or electrolyte excretion (*male rats*). Following i.v. administration to anesthetized dogs, n-docosanol produced little or no effect on the respiratory rate, blood pressure, heart rate and ECG at doses of $\leq$3 mg/kg. Topical and ocular applications of $\leq$3.0 % n-docosanol in male guinea pigs did not demonstrate any local anesthetic activity. *In vitro*, n-docosanol did not show any significant influence on the spontaneous movements of isolated guinea pig ileum (5) or on acetylcholine-, histamine- and barium-induced contractions.

In an *in vitro* penetration study with n-[1-^{14}C]docosanol with the proposed 10 % cream formulation, < 2.0 % of the radio-label was found in the human cadaver skin and < 0.01 % was found in the reservoir fluid. Limited absorption was also observed *in vivo* in both mice and rabbits: < 0.001 % of the radiolabel was found in the plasma of mice, and ~ 2 % of the administered radiolabel was recovered from the skin, plasma and waste products of rabbits. No significant differences were observed in absorption following application to intact and abraded rabbit skin.

Following oral administration, systemic exposures to n-docosanol appeared similar across species and were characterized by non-linear (dose-dependent) kinetics, i.e. increasing the dose of n-docosanol resulted in a disproportionately lower systemic exposure than would have been predicted from a linear relationship. Total absorbed dose following oral gavage with radio-labeled n-docosanol was estimated to be approximately 15 to 20 % . Radioactivity was detected in the plasma within 0.5 hours, with significant levels detected at 1 hour. Peak concentration (C_{max}) varied considerably, 0.5 to 12 hours, but occurred in most animals between 1 and 4 hours post administration. Radioactivity was detected in all tissues examined within 1 day of dosing with the highest levels found in the liver, spleen and brown fat. The half-life of n-docosanol derived radioactivity in the liver was 4-5 days.

By day 1, over 90 % of the radioactivity in the liver was determined to be in the form of polar lipid metabolites. Similar rates of clearance were observed from the spleen. By day 32 post-gavage, most of the tissue-associated radioactivity had been eliminated, with only about 1 % of the original dose localized in brown fat (primarily incorporated as triglycerides) and brain lipids. Metabolism appears to be rapid (nearly complete by 24 hours post-administration) and the pathway appears similar to other fatty alcohols: oxidation to fatty acids (primarily n-docosanoic acid) followed by esterfication to a wide variety of lipids, glycerides and phosphoglycerides which are then appear to be universally distributed in tissues. Following i.v. administration of radiolabeled n-docosanol, approximately 50 % of the radioactivity was excreted in the expired air (presumably as $^{14}CO_2$), 2 % in the urine, 1 % in the feces, and 27 % was present in the tissues 168 hours post-dosing.

Oral doses of 1000 mg/kg/day in rats and 2000 mg/kg/day in dogs for 26 weeks resulted in no discernible toxicity associated n-docosanol treatment. Mean maximum n-docosanol concentrations in plasma (C_{max}) and mean AUC_{0-24} values are presented below.

A: Rats (1000 mg/kg/day)

	Males	Females
C_{max} (ng/ml)	626	529
AUC_{0-24} (ng.h/ml)	3196	2255

B: Dogs (2000 mg/kg/day)

	Males	Females
C_{max} (ng/ml)	1094	2255
AUC_{0-24} (ng.h/ml)	12340	24400

In rabbits, both LIDAKOL 10 % cream and vehicle cream were assigned primary irritation scores of 0.2 when applied to intact rabbit skin, 0.0 when applied to the penis, 2.3 when applied intravaginally (mildly irritating = 0.1-2.0). Increasing the n-docosanol concentration of the cream formulations increased the irritation scores: LIDAKOL 20 % cream resulted in a primary dermal irritation score of 1.11 and LIDAKOL 12 % Cream resulted in an intravaginal irritation score of 2.7. When placed in the rabbit conjunctival sac, LIDAKOL 10 and 20 % creams were both given a primary eye irritation score of 0.25, reflecting conjunctival redness (grade 1) at the end of 1 hour. LIDAKOL 10% cream failed to induce either contact hypersensitivity, photosensitivity or phototoxicity when tested in albino guinea pigs.

Subacute dermal applications (4 weeks) of LIDAKOL 10 % Cream in rabbits at dose levels of up to 1000 mg/kg for 6 hours/day (occluded) on intact and abraded skin or injected directly into the vaginal vault, and subchronic topical applications (13 weeks) in mice at 100 µl (~10 % total body surface area) did not produced any histologic evidence of local or systemic toxicity. Plasma concentrations were generally below the limit of detection in the dermal and vaginal rabbit studies. In mice, where systemic exposure occurred through both dermal and oral absorption, the mean C_{max} concentrations were 205 and 232 ng/ml, and the mean AUC_{0-24} values were 1390 and 1660 ng.h/ml for males and females, respectively.

Reproductive and developmental studies were performed in rats and rabbits with oral doses up to 2000 mg/kg/day. In the rabbit, toxicokinetic analysis on day 14 of gestation revealed C_{max} levels of 142, 46 and 119 ng/ml with AUC_{0-24} values of 945, 667 and 1670 ng.h/ml at doses of 500, 1000 and 2000 mg/kg, respectively. There were no significant effects of n-docosanol treatment in F0 males and females as assessed by clinical behavior and appearance; bodyweight gain; food and water consumption; female estrous cycling; sperm morphology (motility and numbers); mating behavior and fertility index; gestation length, parturition, and lactation; and gross appearance of reproductive

organs (and relative weights) and internal tissues at necropsy. Litter responses, as assessed by numbers of corpora lutea, implantations and viable fetuses, resorption sites, fetal survival, fetal growth, and placental weights were similar in all groups and showed no adverse effects of parental treatment with n-docosanol. Fetal anomalies (visceral and skeletal) observed in treated litters at necropsy were similar in both type and frequency to the concurrent control and/or the historical control data. The general condition of F1 offspring (rats) was similar in all groups with no apparent adverse effects of maternal treatment with n-docosanol. Litter sizes, sex ratios, birth weights and survival rates were similar to controls. There were no dose-related differences in weight gain, physical development, auditory and visual responses, learning ability, neuromuscular function, or reproductive ability. Under the conditions of these study, oral administration of 2000 mg/kg/day n-docosanol was not considered to adversely affect reproduction or to be teratogenic in rats and rabbits.

Vaginal administration of n-docosanol 12 % cream prior to mating did not appear to have a significant effect on either the copulation index or the fertility of rabbits. No maternal toxicity was observed during the study and here were no significant differences in the mean number of corpora lutea, early resorptions or post-implantation sites between the two treatment groups. However, there was a significant difference in the number of viable fetuses and implantation sites in the n-docosanol group compared to the K-Y Jelly group due to a statistically significant increase in the mean pre-implantation loss in the n-docosanol group. However, since a majority of the does in this group did have implants and live fetuses comparable to the controls, it could not be determined if oral administration of n-docosanol may have had an effect on the sperm and/or the fertilized eggs. Further testing would be necessary to resolve this question if the Sponsor were to pursue a vaginally administered product.

Several of the toxicology studies were compromised due to measurable plasma levels of n-docosanol reported in control animals (Study #25 ([redacted]94/LAK002/0706), #26 ([redacted] 94/LAK008/0963), #42 ([redacted]107527) and #50 ([redacted]96/LAK015/0839). For the most part these levels were just above or close to background, however, in studies 42 and 50, control plasma levels were close to the levels found in dosed animals following a single day of dosing. Lidak should address this issue and an inspection of these study sites may be indicated.

Genotoxicity was assessed using the Ames Bacterial Mutation Assay, HPRT Gene Mutation Assay in Chinese Hamster Cells, Chromosome Aberration Assay in Chinese Hamster Cells, and the *in vivo* Micronucleus Assay in Mouse Bone Marrow Cells. Under the conditions used in these studies, there was no indication that n-docosanol had either mutagenic or genotoxic potential.

Carcinogenicity studies were not performed. During a tele-con held on January 123, 1995 between Lidak and Drs. Lauren Black and James Farrelly, HFD-530, Lidak was informed that carcinogenicity studies would not be necessary. However, to be consistent with the requirement of drugs reviewed and approved in HFD-540, I propose, that if LIDAKOL is approvable, Lidak be asked to commit to dermal and photo-cocarcinogenicity studies during Phase 4 of development. This drug product will be used in an area exposed to the sun and for an indication which will necessitate intermittent chronic use (greater than 6 months over ten years). Lidak has argued that his product is already used in cosmetics, particularly lipsticks, however, it has never been previously used as the active ingredient in a drug product or tested for carcinogenicity potential.

AUC levels achieved following oral dosing in animal studies were 2255-3196 ng.h/ml for the rat (1000 mg/kg/day), 1670 for the pregnant rabbit (2000 mg/kg/day), and 12,340-24,400 ng.h/ml for the dog (2000 mg/kg/day). In addition, AUC values in mice, where systemic exposure occurred through both dermal and oral absorption following application of 10% n-docosanol over approximately 10% of the total body surface, the mean AUC values were 1390-1660 ng.h/ml. AUC levels of 503 and 892 ng.h/ml were achieved in healthy human males following a single oral dose of 1000 or 5000 mg n-docosanol, respectively, with no observed adverse effects. Topical application of LIDAKOL 10% Cream to patients with recurrent oral-facial herpes lesions did not result in measurable plasma levels from which to calculate an AUC. However, the Sponsor has estimated the human systemic exposure (maximum plasma concentration) following multiple therapeutic topical doses to be approximately 0.3 to 0.4 ng/ml. The plasma levels of n-docosanol achieved in the animal studies are greater than 1000 fold that expected in humans. Although toxic levels were not achieved in the animal studies, the doses appear adequate to evaluate the potential of n-docosanol to cause adverse effects in humans under the conditions of use described in this NDA.

Proposed Labeling

[redacted]

4 pages of revised draft labeling have been redacted from this portion of the document.

/S/ 5-26-98

Lynnda Reid, Ph.D. Date
Pharmacologist/Toxicologist

cc:
NDA 20-941
HFD-540
HFD-540/Pharm/Reid
HFD-540/Pharm/Jacobs
HFD-540/CSO/White
HFD-540/MO/Okun
HFD-540/Chem/Hathaway
HFD-530/Micro/Biswal
HFD-880/Biopharm/Bashaw
HFD-345/Viswanathan

For Concurrence Only:
HFD-540/DD/JWilkin /S/ 5/29/98
HFD-540/TL/AJacobs 5/26/98

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AUG 10 1998

n-Docosanol 10% Cream
NDA 20-941
Lidakol® 10% Cream
Reviewer: E.D. Bashaw, Pharm.D.
APW

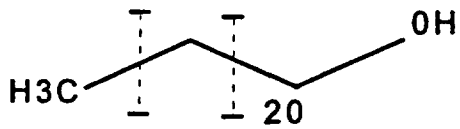
Lidak Pharmaceuticals
La Jolla, CA 92037

Submission Date:
Dec. 23, 1997

Review of an NDA

I. Background

Lidakol® (n-docosanol, behenyl alcohol) is a naturally occurring fatty alcohol. It is a 22-carbon straight chain saturated alcohol with a formula of $C_{22}H_{46}0$ and a molecular weight of 326.61. It is a white solid and is soluble in chloroform, slightly soluble in ethanol and insoluble in water. It has the following general structure:



n-Docosanol is a broad spectrum anti-viral agent having topical activity against lipid-enveloped viruses including herpes simplex virus 1 & 2 (in vitro and in vivo), and varicella zoster, cytomegalovirus, human herpes virus 6, influenza A, and the human immunodeficiency virus (HIV-1) in vitro. It is being developed as a topical anti-herpes simplex virus (HSV) agent for the management of recurrent outbreaks of fever blisters/cold sores. It's mechanism of action is related to its ability to block one or more of the steps of viral entry into a cell. In vitro it has been shown to block the fusion of the viral envelope with the cellular membrane of normal cells. By blocking viral entry to the cell it effectively inhibits viral replication. It is this mechanism of action that explains it's wide spectrum of activity against lipid-enveloped viruses that utilize fusion as the sole or major mechanism of entry into the cell. This mechanism of action also makes the development of resistant strains of the virus highly unlikely as it exerts its action at the mammalian cell wall and not against the viral sub-unit itself. In this product it is formulated as a 10% cream for topical administration.

II. Recommendation

In this NDA the applicant has submitted the results of one in vitro and three in vivo pharmacokinetic studies. The in vivo studies included oral administration of a radiolabeled dose of n-docosanol, oral and topical administration of n-docosanol in healthy males, and topical administration in patients with oral facial HSV infection. The results of these studies indicate that n-docosanol is minimally absorbed with only 1 sample out of 208 samples having detectable levels in the plasma after dosing with the to-be-marketed formulation. From a biopharmaceutic standpoint the sponsor has adequately addressed the issues of systemic absorption/bioavailability and the application is acceptable from a Clinical Pharmacology/Biopharmaceutic standpoint.

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III. NDA Overview

As noted in the background section, this NDA consists of three in vivo and one in vitro study. Only 1 of the in vivo studies examined the issue of systemic absorption of n-docosanol in patients with oral-facial HSV infection. The other two studies, conducted in healthy adults, deal with the disposition and metabolic fate of n-docosanol following topical and oral ingestion of both cold and radiolabled doses.

Formulation

In this NDA the active ingredient, n-docosanol, is formulated as a white, non-staining, 10% cream. Reproduced below is its quantitative and qualitative formulation.

Ingredient	Percent	Formula
n-Docosanol	10%	
Sucrose Stearate and Sucrose Distearate		
Light Mineral Oil,		
Propylene Glycol,		
Benzyl Alcohol,		
Purified Water,		

As Lidakol® the cream will be available in the market as a 2, 5, and 15gm tube.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

[redacted]

V. General Pharmacokinetics (In Vivo)

Study #95-LID-01

"Excretion Balance, Pharmacokinetic and Metabolism Study after a Single Oral Dose of 14C-Labeled n-Docosanol in Healthy Male Volunteers"

Objective: The objective of this study was to determine the systemic absorption of n-docosanol following the administration of a radiolabeled dose of docosanol to healthy male subjects.

Investigator: J.J. van Lier, M.D.

Study Site: [redacted]

Treatments: 1000mg n-docosanol [redacted]
2 patients received 5 µCi of ^{14}C labeled docosanol
4 patients received 15 µCi of ^{14}C labeled docosanol

Methods

This study was initiated to investigate the systemic availability of docosanol and to identify routes and possible mechanisms of drug elimination. A total of six healthy adult males were enrolled and completed all phases of this trial.

Demographics of Enrolled Subjects

N=10	Mean (%CV)	Range
Age (yrs)	25 (36%)	42-19
Weight (kg)	72 (14%)	83.6-59.1
Height (cm)	185 (4.3%)	195-175

The study was split into two phases using different levels of radioactivity. Initially two subjects were dosed with 5 μCi of ^{14}C labeled docosanol and the disposition of radioactivity was monitored. Due to the low levels of systemic radioactivity detected it was decided to dose the remaining four subjects with higher doses of radioactivity (15 μCi) so that it might be possible to quantify systemic absorption.

Despite the two phases of the trial all subjects followed the same dosing and sampling protocol. Following a 10 hour fast all subjects were given their dose of docosanol (5g of a 20% dispersion) in [redacted] Following dosing, extensive blood sampling was initiated according to the following schedule:

For total radioactivity (plasma)
10ml blood samples were collected and separated pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours post dose

For total radioactivity (whole blood)
1ml blood samples were collected pre-dose and at 1, 2, 3, 4, 12, 24, 48, and 168hrs post-dose.

Metabolic profiling
20ml blood samples were collected at 4 and 24 hours post-dose for profiling purposes.

In addition to the blood and plasma, urine was collected following a pre-dosing void over the following intervals: 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144, 144-168hrs. All feces were also collected over the 168hr period following dosing.

Expired CO_2 was also analyzed for ^{14}C pre-dose and at 2, 4, 8, 12, 24, and 48hrs post-dosing.

Results
Reproduced below is a summary table of the cumulative excretion data collected in this study. In general total excretion of drug was completed by 96hrs post-dose.

Amount Excreted (Ae) as % of labeled dose

N=6	Ae urine	Ae feces	Ae air	Ae total
Mean (%CV)	0.028 (175%)	103.73 (3.8%)	0.907 (44%)	104.68 (3.8%)
range	[redacted]			

The results of this study clearly indicate that there is a low degree of systemic absorption of docosanol following oral administration. Metabolic profiling of the feces revealed that approximately 80% of the excreted compound was docosanol and 8% was docosanoic acid (the corresponding carboxylic acid to the alcohol). The remainder was unidentified polar and non-polar compounds. Following hydrolysis these ratios changed to 68% for docosanol and 28% for docosanoic acid, suggesting that these previously unidentified metabolites were glucuronides or other conjugates of both docosanol and docosanoic acid.

A similar attempt at metabolic profiling of the urine and plasma results were unsuccessful as the amounts of detectable species present in these samples were too low to reliably quantify. As the fractional recovery of radioactivity clearly indicates that fecal excretion is the primary route of elimination, it is unlikely that either matrix has significant amounts of any additional unidentified metabolites.

Study Conclusions

The results of this study indicate that docosanol has a low degree of absorption following oral administration and that it is almost completely recovered as either unchanged drug or as the corresponding organic acid (to the alcohol). While small amounts of ^{14}C were detected in the expired air and in the plasma, these amounts account for <1% of the total dose of 1gm.

Study #94-LID-01

"A Combination of a Single-Dose Topical Study with n-Docosanol and a Single Rising-Dose Oral Study with n-Docosanol in Healthy Male Volunteers"

Objective: The objective of this study was to determine the systemic absorption of n-docosanol as a 10% cream to two oral doses of docosanol in healthy adult males.

Investigator: I.J. Terpstra, M.D.

Study Site: [redacted]

Treatments: Phase 1-10g of 10% docosanol topical cream (1g total dose)
Phase 2-5ml of 20% docosanol [redacted] dispersion (1g total dose)
Phase 3-25ml of 20% docosanol [redacted] dispersion (5g total dose)

Methods

This study was designed as non-randomized three-period crossover comparative bioavailability study. A total of six healthy males were enrolled in this study and all subjects completed the study (although one subject was excluded from phase 2 due to the flu). The demographics for these subjects is reproduced below:

Demographics of Enrolled Subjects

N=6	Mean	Range
Age (yrs)	23	25-22
Weight (kg)	82	87-77

Upon enrollment in the trial the subjects were required to spend three 3 day periods in the clinical study unit. At 9am on the morning of the second day the subjects were dosed with the appropriate formulation/dose for that period. As noted earlier this was NOT a randomized trial. All subjects received all phases in a 1-2-3 order with a 1 week washout period between phases.

For Phase 1 the subjects had 10g of cream applied to a 12 x 12 cm patch of skin on their lower back. Following drug application the area was covered with an occlusive dressing (Actiderm®) for 24 hours. After 24 hours the covering was removed and the area was cleaned with lukewarm water to remove any cream remnants.

For Phases 2 and 3 the subjects were given either 5 or 25ml of a 20% dispersion of docosanol in [redacted] water. Each dose was followed with 200ml of water to ensure full dosing.

During each treatment blood samples (10ml) were collected at 1, 2, 4, 6, 8, 12, 14, 24, 36, and 48 hours post-dosing. In addition urine samples were collected over the 0-12 and 12-24 hour post-dosing interval, however, in light of the low urinary recovery found in the radiolabel study (LID-01, page 5) these samples were not analyzed.

Results

Analysis of the plasma samples from Phase 1 (topical application) yielded no plasma levels above the limit of detection (10ng/ml). During Phases 2 and 3 low plasma levels were detected and are summarized in the following table:

Oral Absorption Data-Mean (%CV)

	AUC_{0-48} (ng*h/ml)	Cmax (ng/ml)	Tmax (hr)	$Cl_{po/F}$ (l/min)
Phase 2; 1g dose	172 (122%)	19 (95%)	8	201 (90%)
Phase 3; 5g dose	713 (116%)	124 (96%)	6	410 (149%)

The results from this study are highly variable with coefficients of variation >90% for all calculated parameters. This variability is due in some part to the small number of subjects present in this study (5 subjects in Phase 2, and 6 in Phase 3). Even so it is unlikely that the data would be improved if more subjects were used. This is due in no small part to the poor bioavailability of docosanol following oral administration. What is surprising is that even with the large CV's, the data is roughly dose proportional for both AUC and Cmax. As for the observed difference in clearance values, this can be explained by the fact that Cl here is apparent oral clearance (Cl/F) and with drugs with low bioavailability, any variance in F will tend to exaggerate apparent Cl differences. Given that F is probably very low this would account for the observed difference in clearance.

Study Conclusion

The results of this study confirm the previous radiolabel study in that the observed plasma levels are low and erratic. While there does appear to be a "rough" degree of dose proportionality, the

small number of subjects and the high intersubject variability (%CV) makes this conclusion provisional-at best.

Study #95-LID-02

"Pharmacokinetic Study to Assess Plasma Levels of n-Docosanol after Single-Dose and Repeated Topical Dosing with n-Docosanol 10% Cream in Healthy Volunteers with Herpes Labialis Recurrence"

Objective: The objective of this study was to determine the systemic absorption of n-docosanol as a 10% cream in patients with oral-facial Herpes Labials.

Investigator: L. Habbema, M.D.

Study Site: [redacted]

Treatments: 10% n-docosanol cream[1] (Lot# GL019L-95D)

Methods

As noted above this study was designed to assess the systemic absorption of n-docosanol in patients with Herpes Labials. A total of 18 healthy subjects with herpes were screened in the trial and a total of 10 subjects (all female) were enrolled in the trial.

Demographics of Enrolled Subjects

N=10	Mean (%CV)	Range
Age (yrs)	34.1 (38%)	59-22
Weight (kg)	68.9 (13%)	80-55
Height (cm)	169 (4.2%)	182-161

Subject selection for inclusion included the normal requirements (otherwise healthy subjects with herpes labials) and that they have an active recurrence of disease. All screened subjects were instructed to come to the study center upon recognizing the first symptoms of recurrence (burning, tingling, pain, redness, etc.). After re-confirming subject suitability the subjects were released from the study unit with instructions to return when the vesicles appeared.

Once the vesicles appeared the subjects returned to the unit (day 1 of the study) and the vesicles were ruptured using a 21 gauge needle. Following vesicle rupture 10% docosanol cream was applied to the affected area by the investigator. Blood samples (5ml) were collected over the next 24 hours at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours for docosanol levels. Following the 24 hour blood sample the subjects were released from the study unit and instructed to apply the test cream to the affected area 5 times a day (at 4 hour intervals) for the next two days. On day 4 of

[1] To-be-marketed formulation

the study the subjects returned to the study unit and following another application blood samples were again collected at the same timepoints as used on day 1.

Results

A total of 209 blood samples were collected and analyzed for the presence of docosanol. Of these only 1 sample was positive for docosanol at the limit of detection of 10ng/ml. All of the other samples were negative for docosanol.

Study Conclusions

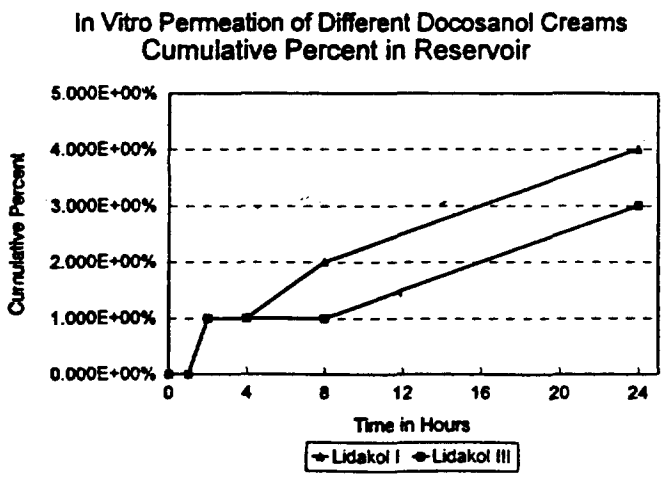
The results of this study suggest that docosanol is not significantly absorbed topically in subjects with active herpes labials. This is not a surprising finding given that docosanol is a long chain unsaturated alcohol with a molecular weight over 300 and is insoluble in water.

VII. Supportive In Vitro Studies

In Vitro Permeation of radiolabeled n-docosanol 10% Cream

As a complement to the in vivo pharmacokinetic studies the sponsor undertook an in vitro assessment of dermal penetration using Franz diffusion cells and cadaver skin. A total of 16 test chambers were prepared using split thickness (200 micron) human cadaver skin. Of these 16 chambers 8 used a developmental formulation of docosanol cream (a/k/a Lidakol I) and the to-be-marketed cream (a/k/a Lidakol III). The reservoir chamber was filled 6-10ml of 4% bovine serum albumen isotonic buffered saline solution. A total of 10mg/cm^2 of ^{14}C-labeled docosanol 10% cream (containing 55µCi) was applied to the skin in each test chamber.

During the study 1ml samples were collected from the reservoir side of each test chamber at 0, 1, 2, 4, 8 and 24 hours with fresh replacement. At the end of the observation period, the skin tissue was cleaned with gauze and warm water to remove any remaining cream. Following this the stratum corneum from each skin sample was removed using skin stripping (~22 strips) and the dermal and epidermal layers were split for individual analysis. The results from this study are summarized below:



Total Percent Recovery

	Reservoir	Dermis	Epi-dermis	Tape	Gauze	Wash	Total
Lidakol I	0.004	0.02	0.4	0.5	1.8	78.3	81
Lidokol III*	0.003	0.04	0.7	1.2	3.9	63.8	69.7

*To-be-marketed cream

The results of this in vitro study confirm the results of the in vivo studies, namely that the dermal penetration of docosanol is minimal and appears to be limited to the dermis and stratum corneum (tape data in table above). A limitation of these types of studies is that the skin tested is normal skin, i.e, the effect of disease state is not assessed. While this is true, it is also true in this case that the in vitro permeation data is consistent with that seen in patients. The net result from this study is that if docosanol cream is inadvertently applied to normal healthy skin, there will be minimal if any absorption beyond the top layers of the skin.

VIII. Labeling

At the present time the application for topical docosanol cream is deficient from the medical standpoint. As the sponsor will be asked to undertake new clinical trials a review of the labeling will be deferred at this time.

IX. Conclusions

From our review of the submitted information the following conclusions can be drawn:

1. Docosanol cream is minimally absorbed following topical administration to either diseased or healthy skin.
2. Low amounts of docosanol are absorbed systematically following oral administration. As herpes labials is a disease found on, in and around the mouth it is likely that small amounts will be inadvertently swallowed. Even so the amounts are highly variable and low even with systemic administration of large doses (1 and 5g).
3. While a formal analysis of gender was not undertaken by the sponsor, the inclusion of male and female subjects in the development of this product (albeit in separate studies) did not reveal a significant gender effect.
4. In vitro studies revealed that, in healthy cadaver skin, docosanol penetration was limited primarily to the stratum corneum and epi-dermis, with very small amounts present in either the receptor fluid or the dermal layers.

X. Comments

1. In future studies with this or other products the sponsor needs to consider using larger number of subjects. In this NDA it was only the fact that there was essentially no systemic absorption that allowed the sponsor to use the number of subjects in their trials that they did. Had there been significant systemic absorption these studies would have been judged to be supportive and not pivotal in nature and design.

/S/ 8/10/98

E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-550)
Division of Pharmaceutical Evaluation-III

Secondary Review, Arzu Selen, Ph.D. /S/ 8/10/98

CC: NDA 20-941 (ORIG),
HFD-540/DIV File
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HFD-344(Viswanathan)